

From the Medical Clinic of the University of Zürich
(Director: Professor Dr. *W. Löffler*)
Thesis done under the guidance of P.D. Dr. *S. Moeschlin*

The Guillain-Barré Syndrome in Infectious Mononucleosis

A Survey of the Literature and Study of a Fatal Case

Inaugural Dissertation

For the Degree Doctor of Medicine from the Medical Faculty
of the University of Zurich

Presented by
Melvin KLEIN
of New York, U.S.A.

Accepted on the proposal of Prof. Dr. *W. Löffler*
and P.D. Dr. *S. Moeschlin*

Zurich 1954



S. Karger Publishers, Basel



Reprint from Confinia Neurologica, Vol. 14, No. 4 (1954)

With Gratitude
To my Parents

Introduction

The neurological complications of infectious mononucleosis present varying clinical pictures. In general they are lymphocytic meningitis, encephalitis (meningoencephalitis, encephalo-myelitis), Guillain-Barré syndrome (polyradiculitis-polyneuronitis) and neuritis in order of frequency.

This paper will present a survey and summary of those cases of infectious mononucleosis in the literature that were complicated by the Guillain-Barré syndrome, including the clinical and pathohistological study of a fatal case observed in the University Medical Clinic of Zurich.

The etiology of the Guillain-Barré syndrome is unclear. The symptoms have been seen to develop, following a bacterial or viral infection, an intoxication, and also with no apparent previous illness. It is therefore of diagnostic interest to present the association of this syndrome to infectious mononucleosis which in recent years has been shown to be a disease of an extreme protean nature. The etiology of

* Work under the Guidance of P.-D. Dr. S. Moeschlin.

infectious mononucleosis is also inconclusive, evidence indicating a virus. There is conclusive evidence however, that it is a generalized infectious disease involving the reticuloendothelial system and capable of producing pathological symptoms and lesions in all organs.

The cases of interstitial pneumonia, liver damage, heart lesions and kidney involvement are but some of the numerous reports in the literature. These are supported by liver, spleen, and bone marrow puncture and autopsy material when available. Primarily mononuclear cell accumulations and hyperplasia of the reticulum is found. In the case to be presented here such cell accumulations were found in the nerve roots and spinal ganglia. Comparison will be made to the lesions found in two similar fatal cases as well as to the pathological changes generally found, as reported in an extensive study of fatalities from Guillain-Barré-Landry paralysis which were not involved with infectious mononucleosis.

Part I. Review of the Literature

Historical

In 1885 *Filatow* and then somewhat later *Korsakoff* described a disease that *E. Pfeiffer* in 1889 named glandular fever. It is important to note that he recognized the disease as a generalized infection with painful swelling of the lymph nodes, difficulty in swallowing, enanthem and enlargement of the liver and spleen. Subsequent observers reported nephritis and exanthem as additional symptoms.

A more accurate diagnosis was made possible only after the characteristic blood pictures began to be studied. In 1907 *Türk* published a case of an angina patient with the blood picture of what appeared to be a lymphatic leukemia.

As other cases were reported attention was focused on the blood alterations. In 1908 *J. E. Burns* clearly described the lymphocytosis in two epidemics of glandular fever. This work was completely overlooked. In 1920 *Sprunt* and *Evans* published their study "Infectious Mononucleosis" as a new disease entity with the blood pictures observed. It was *Tidy* in 1921 who wrote that glandular fever and infectious mononucleosis were the same disease.

In Europe, *Glanzmann*, *Chevallier*, *Lehndorff* und *Schwarz*, in 1928 began to publish extensively, correlating exhaustive hematological studies to their investigations, differentiating various blood forms. In 1932 *Paul* and *Bunnet*, utilizing a test developed by *Hanganatziu* and *Deicher* were able to show the presence of heterophile antibodies in patients with infectious mononucleosis. The development of the serum reaction enabled a more accurate diagnosis.

Neurological Complications

Longcope in 1922 and *Glanzmann* in 1930 suspected encephalitis as a possible complication of infectious mononucleosis. However it was

Survey of the Literature

Author	Age	Sex	General Signs	Neurological Signs	Spinal Fluid	Outcome
Zohman and Silberman (1942)	21	M	Generalized lymphadenopathy, typical blood picture. Heterophile titer off.: 1024. Incub. 21 days.	Headache, nuchal rigidity, irritability, myoclonic and athoid movements, flaccid paralysis of all extremities, absence of all deep reflexes plus occasional fasciculations. Ability to move only fingers and toes. Generalized pain in extremities and back, marked tremors and perspiration, difficulty voiding, ptosis of right lid, left peripheral facial paralysis, nasal speech.	Pressure 130, clear and colorless, 4 cells, albumin pos, slight globuline.	Recovery was not complete. Motor weakness and left foot drop remained.
Hiller and Fox (1943)	17	M	Generalized lymphadenopathy, splenomegaly, typical blood picture. Heterophile agglutination 1:256. Incub. 2 to 3 days for meningeal signs, flaccid paralysis 5 days later.	Nuchal rigidity, Kernig and Brudzinsky signs positive, diplopia, rt. facial weakness, speech difficulty, complete flaccid paralysis, reflexes absent, defecation absent.	Protein 360, 2 cells, globuline strongly positive, sugar 63, chlorides 731, colloidal gold curve flat.	Completely recovered in about one month.
Coogan Martinson and Mathews (1945)	36	M	Sore throat, typical blood picture, Heterophile antibody 1:2048. Incub. 10 days.	Pain down both arms with weakness and inability to move left arm away from side. Atrophy of the deltoid and shoulder muscle groups.	6 cells, Pandy pos. Total protein 100.	Complete recovery in 2 months.

<i>Geliebter</i> (1946)	10	F	Cervical adenopathy, typical blood picture. Heterophile antibody of 1 : 256. Inc. 28 days.	Headache, nuchal stiffness, positive Kernig, pain in both hips and shoulders, general weakness in all muscle groups, inability to sit without support, all deep reflexes, diminished to absent, hyperesthesias and transient diplopia.	Increased pressure, 9 lymphocytes, 6 red cells, total protein 400, globulines strongly positive, chlorides 740.	Complete recovery in 51 days.
<i>Slade</i> (1946)	36	M	Generalized lymphadenopathy, typical blood picture, and heterophile antibody titer 1 : 112. Incub. 17 days.	Headache, bilateral facial hyperesthesia, anaesthesia of the chin, dysarthria, absence of the gag reflex, paresis of the masseters and pterygoids, generalized muscular tenderness and weakness, adiodokinesis, deep reflexes absent to diminished, abdominal and cremaster absent, absent plantar response, right foot drop.	2 cells protein 48.	After 150 days incomplete recovery, diminished deep reflexes, slight facial weakness.
<i>Richter et al.</i> (1947)	22	M	Cervical adenitis, typical blood picture, heterophile antibody titer of 1 : 1792. Incub. 12 days.	Headache, nuchal rigidity, tingling and numbness of the hands and feet with right peripheral facial paralysis. Moderately depressed gag reflex, difficulty in swallowing, hyperesthesia of the hand and feet, flaccid paralysis of all the extremities, absence of all deep reflexes, respiratory paralysis, and convulsions.	36 cells, (94% lymph.) Protein 81.	Patient died. Autopsy showed evidence of infectious mononucleosis. Accumulations of small round cells, mononuclear cells and eosinophiles were noted in the anterior nerve root.

Author	Age	Sex	General Signs	Neurological Signs	Spinal Fluid	Outcome
<i>Ricker et al.</i> (1947)	21	M	Cervical adenitis suggestive blood picture, heterophile antibody titer not done. Incub. 18 days.	Soreness and weakness of the lower extremities, weak action in the lower third of the thorax, definite weakness of the upper extremities, paralysis of the trunk and lower extremities, transient paresthesias of the feet, hands and legs, all deep and abdominal reflexes absent. Respiratory paralysis.	8 cells, protein 74, sugar 50, chlorides 627.	Patient died. Autopsy showed evidence of infectious mononucleosis. Cellular infiltrations of the nerve roots noted at all levels.
<i>Graham, Schwartz and Chapman</i> (1949)	18	M	Patient was acutely ill. Lymphnodes in inguinal and axillary regions enlarged. Typical blood picture, heterophile agglutination 1:7156.	Weakness of the shoulder girdle and arms (especially the left), inability to raise the trunk, nuchal rigidity, Kernig bilaterally positive, paralysis of the extremities, and muscular pain. Deep reflexes hypo-active to absent, cremaster reflex absent, inequality of the abdominal reflexes, hyperesthesias of the arms, legs and buttocks, left facial paralysis and anesthesia.	Pressure 150. No cells, protein 70, sugar 88.	Recovery in 6 weeks.

<i>Dolgopol and Husson</i> (1949)	19	F	Malaise, fatigue and weakness of the legs. Sore throat, generalized lymphadenopathy and palpable spleen. Blood picture showed 49% lymphocytes (11% abnormal). Heterophile antibody 1:1792 positive.	Photophobia and diplopia. Headache and meningismus developed. Positive Kernig and Brudzinski signs. Inability to move legs, absence of all tendon reflexes. Abdominal reflex present. Difficulty in swallowing. In terminal stage stupor.	At the end of the first weeks 50 cells and no increase in protein, increased pressure.	Patient died after 9 days of illness. Some degenerative changes and perivascular hemorrhages were seen in the central nervous system.
<i>Klovstad</i> (1950)	6	M	Fever, generalized lymphadenopathy, typical blood picture, monocytoïd cells 88%. Paul Bunnell not done.	The child could not stand or walk, Achilles and patellar reflexes absent, flaccid paralysis of the extremities, peripheral facial hemiparesis.	No cell increase, protein clearly increased	The facial paralysis lasted 2-3 weeks. The paralysis of the lower extremities longer.
<i>Creuuro</i> (1950)	17	F	Lymphadenopathy typical blood picture, fever, enanthem, tonsils enlarged, heterophile agglutination 1:1280.	Headache, nuchal rigidity, all deep and abdominal reflexes absent, flaccid paralysis of the legs and partially of the arms, patient unable to sit, diminished sensibility below the knees, complete facial paralysis, palatal paralysis, speech impaired and nasal.	Spinal fluid clear, Pandy strongly positive, protein 168mg% sugar 66, chloride 732, not cells.	Complete recovery in 3 months.

Author	Age	Sex	General Signs	Neurological Signs	Spinal Fluid	Outcome
<i>Silversides and Richardson</i> (1950)	24	M	Lymphadenopathy, spleen palpable, fever, reddened pharynx, typical blood picture (67% atypical lymphocytes) Paul-Bunnell 1:40 positive.	Headache, nuchal rigidity, weakness of all muscle groups in both lower limbs, sensation to pain and touch was impaired below the 7th dermatome, difficulty in micturition, 3 attacks of generalized convulsive seizures, abdominal and tendon reflexes absent	Spinal fluid pressure 230 mm, protein 64 mg%, 29 cells, all lymphocytes.	Recovery in 6 weeks.
<i>Owen</i> (1952)	33	F	Lymphadenopathy, fever, chills, nausea. Typical blood picture, heterophile titer 1:64 positive, liver enlargement and tenderness.	Headache, complete left facial paralysis, pain and weakness of the legs, absence of tendon reflexes.	Protein 75 mg% chlorides 760, sugar 72, 4 cells.	Complete recovery in one month.
<i>Nixon</i> (1952)	41	F	Mandibular lymph nodes, fever, extreme malaise, typical blood picture, spleen enlarged and tender.	Weakness of both legs, paresthesias of both arms, gradual progression to complete quadriplegia, loss of pain touch and temperature sensation to T. 3, dyspnoea, absence of all reflexes, facial paralysis, acute psychosis and an epileptiform attack.	Protein 82 mg%, no cells.	Patients died after a hospital course of almost 5 months.

Nixon (1952)	27	F	Submandibular and supraclavicular nodes, liver and spleen enlarged blood picture showed a few atypical leukocytes. Heterophile titer repeatedly positive 1:56.	Quadruparesis, bilateral ankle clonus and Babinski reflexes, positive Hoffmann signs, sensibility disturbances of the left leg progressing to a flaccid paralysis of the legs, paresis of the forearm extensors, hyperesthesia in both arms, tendon reflexes absent in arms.	Protein 68 mg%, 4 cells. Neurological symptoms persisted at the time of the report.
Garvin (1953)	18	M	Generalized lymphadenopathy inflamed pharynx, typical blood picture, positive heterophile antibody titer of 1:224.	Ptosis of the right eye, weakness of the right masseter, tongue protruded to the right, weak arm movements, especially right, weakness of the lower extremities, hypalgnesia and hypesthesia on the arms and feet, tendon reflexes absent, abdominal and cremaster reflexes absent.	Pressure 200 mm. Complete recovery in 4 weeks. protein 900 mg%, sugar 45, 3 cells lymphocytes.
Fiese, Cheu and Radding (1953)	58	M	History of sore throat two months previous. Cervical lymph nodes enlarged, but indolent. Blood picture two months after onset showed no typical changes. Heterophile agglutination 1:1792 positive.	Symptoms developed 1 week after begin of illness. Swallowing difficult, hearing impaired, diplopia. Locomotor disturbances, paresthesias and hypesthesias of the extremities. Muscle action weak, coordination poor. Tendon and abdominal reflexes absence.	Protein 200 mg%, no cells. Complete recovery in 3 months. Residual numbness of the soles.

Note: Since this survey was made three more cases of *Guillain-Barré* syndrome with infectious mononucleosis have been reported by M. Rafferty, E. E. Schumacher Jr., G. O. Grain and E. L. Quinn in the A. M. A. Archives of Internal Medicine 93, 2, February, 1954.

not until the case of *Epstein* and *Damashek* which appeared in 1931, that the involvement of the nervous system was demonstrated. They described the following case (briefly summarized):

A 19-year-old boy with the blood picture of infectious mononucleosis, lymphadenopathy, splenomegaly and redness of the throat was admitted to the hospital. Neurological symptoms which presented themselves were headache, irritability, ptosis of the right eye, weak pupillar reaction, nuchal rigidity, clouded sensorium, hyper-reactive reflexes and positive *Kernig* and *Oppenheim* signs. Spinal fluid showed a fluctuation of the cells between 30 and 40 at the height of the disease and the protein was 0.052 gm%.

These authors correlated the infectious mononucleosis and posed the question of which was primary. They tended to believe that both conditions were due to the same infectious agent based on the parallel course of the spinal fluid cells and the leukocyte counts, and also the simultaneous clinical healing. This was the first case to appear in the literature correlating nervous system symptoms to infectious mononucleosis. Other cases appeared shortly thereafter in rapid succession. Cases observed by *A. Hecht Johansen* further confirmed such neurological complications. In the medical clinic of Zürich three cases between 1935 and 1937 were described by *Huber*, two with pathological liquor changes. As the literature concerning nervous system involvement grew, the Guillain-Barré syndrome was seen as one such complication. In general the frequency of neurological complications in cases of infectious mononucleosis is 0.37 % as reported by *Silver-sides* and *Richardson*.

The Guillain-Barré syndrome was described in its typical symptomology of symmetrical motor weakness, unilateral facial paralysis, hyper- and hypesthesias, by *Guillain*, *Barré* and *Strohl* in 1916, with emphasis on the albumino-cytologic dissociation.

Survey of the Pathology

Few patients come to autopsy but the material thus far observed, based on the two reports by *Ricker*, shows similar changes to the case reported in this paper. In general these are a generalized hyperplasia of the mononuclear cells and the reticulo-endothelium. These findings were extensively corroborated with the material obtained during the course of the disease. *Downey* and *Stasney* made observation on excised lymph nodes and likewise *Gall* and *Stout*.

*Pathology Report of Two Fatal Cases of Infectious Mononucleosis
with Guillain-Barré Syndrome*

Ricker et al. in an examination of two fatal cases of *Guillain-Barré* associated with infectious mononucleosis found congestion of the leptomeninges and moderate accumulations of mononuclear cells in the arachnoid. In the interfascicular perineurium particularly perivascularly, in the anterior nerve roots, there were accumulations of small round cells, scattered larger mononuclear cells and a few eosinophiles.

In a second patient the leptomeninges were edematous with a few accumulations of lymphocytes and large mononuclear cells with engorgement of the capillaries and veins throughout the nervous system. There were small perivascular hemorrhages in the gray matter of the lower cervical cord.

Ganglion cells throughout the cord showed vacuolization, early chromatolysis, decreased eosinophilia of the cytoplasm and dispersion of the nuclear chromatin. Sections from the nerve roots showed marked congestion and edema of the nerve fasciculi. Cellular infiltrations were noted at all levels, in the anterior nerve roots, but particularly in the cauda equina. Bodian stains revealed marked distortion of the axis cylinders. Myelin sheaths were swollen and disrupted. Sections of the femoral nerve revealed an infiltration consisting predominantly of lymphocytes, although large numbers of mononuclear cells were present, particularly perivascularly. Sections of the facial, acoustic and phrenic nerves showed some infiltrations. The trigeminal nerves appeared normal. These two reports were probably the first fatal cases of infectious mononucleosis showing the *Guillain-Barré* syndrome to appear in the literature.

Pathology Report of Fatal Guillain-Barré Syndrome Cases

It is interesting to compare the previous reports to an autopsy report of three fatal *Guillain-Barré* syndrome cases without clinical infectious mononucleosis by *Sabin* and *Arning*, describing the following lesions in the adrenals, liver, kidney and heart.

The lesions in the adrenals were focal degeneration and infiltration with mononuclear cells; those in the liver consisted of cellular infiltration in the capsule and portal spaces, focal necrosis of cells with cellular infiltration and focal fatty degeneration; those in the kidneys consisted of focal intertubular infiltration with mononuclear cells and those in the heart were interstitial infiltration with mononuclear and polymorphonuclear cells.

The diffuse nature of these lesions is very similar to what is found with infectious mononucleosis. This is further shown in an extensive study of fifty fatal cases of the *Landry-Guillain-Barré* syndrome by *Haymaker* and *Kernohan*. In eight cases the spleen showed the typical blood picture found with infectious mononucleosis, but in only two was infectious mononucleosis clinically diagnosed (the two cases re-

ported by *Ricker*). This consistent similarity very strongly indicates that the same mechanism or the same or at least a related infectious agent is responsible for both.

The report of *Haymaker* and *Kernohan* enables a progressive study of the pathological changes in the nervous system depending on the length of illness before the patient died.

After 4 days: Interstitial edema and swelling of the neural sheaths.

After 5 day: Fragmentation of the sheaths and swelling of the axon cylinders.

After 9 days: Further disintegration of the sheaths and axon cylinders and occasionally lymphocytic infiltrations.

After 11 day: Phagocytes occur.

After 13 days: Proliferation of the Schwann cells.

After 46 days: In some areas the entire axon cylinders were gone. The entire process was most marked where the anterior and posterior nerve roots joined, the lesions decreasing proximally and distally from that point. The vessels as a rule were unaltered. In the spinal ganglion lymphocytic infiltrations were occasionally seen.

Cranial nerves were involved in 47 cases. In all the cases of Guillain-Barré with infectious mononucleosis cranial nerve involvement was noted (refer to Survey).

Pathology of Fatal Cases of Infectious Mononucleosis

The relatively few cases that come to autopsy show essentially the same mononuclear cell accumulations in the visceral organs. Death can result from involvement of the lungs in the form of interstitial pneumonia, renal, hepatic, or cardiac failure, and of course central nervous system involvement.

Custer and *Smith*, on the basis of nine autopsies of infectious mononucleosis patients, are of the opinion that the diffuse lesions in the various organ systems consisting of lymphocytic "infiltrates" are metaplastic rather than inwandering; that they are formed in situ from cells of the reticulo-endothelial system.

Bradshaw reported a case of mitral stenosis following infectious mononucleosis, but *Contratto*, in a study of 196 cases did not find any cardiac abnormality developing.

Part II. Personal Investigations

Case Report

The patient was a 32-year-old male.

Anamnesis: In early childhood the patient developed a rachitic kyphoscoliosis. There were no other serious illnesses.

June 30, 1948: The patient felt a burning sensation in his back and shoulder

regions and especially in the sacral area. The man was tired, unable to work and developed chills and sweating. Temperature was not measured. A physician was called on July 4 because the symptoms persisted.

July 6: A severe headache developed in the occipital region with pain radiating to the neck. The patient vomited three times, the headache lasted two days.

July 9: The patient felt subjectively well enough to voice the desire to resume work.

July 10: Toward evening the patient felt a weakness in both legs, more so the right. His walk was uncertain and he had cramp-like pains in both thighs.

July 11: The patient collapsed when he attempted to walk, he could barely sit upright.

July 12: A weakness of both upper arms developed, especially the left. The patient could no longer stand or sit. He had no double vision and micturition and defecation were normal. Respiration and swallowing were normal. The patient was admitted to the hospital.

Physical Examination: The patient was in a supinated position and apathetic. He was muscularly poorly developed and showed a severe kyphoscoliosis. There were no signs of meningeal irritation and the cranial nerves were intact. The tonsils were moderately enlarged, strongly fissured, and showed many small yellow spots that could be easily and painlessly wiped off.

Lymphatic System: In the right submandibular region two pea-sized nodes which, were sharply defined, mobile and painful upon pressure, were palpated. Bilateral cervical chains of nodes, and also in the supraclavicular, axillary and inguinal regions, enlarged nodes were palpated. All were of increased consistency, smooth, moveable, clearly defined and somewhat painful.

Abdominal Organs: The liver was enlarged, smooth, of increased consistency and indolent. The spleen was palpable at least 3-4 cm. below the arcus, of increased consistency and indolent.

Neurological Examination: Upper extremities: The shoulder girdle musculature was paretic, notably more so the left. The left arm could be raised to approximately 80 degrees. The tonus was decreased, the coordination intact.

Trunk: There was a complete paralysis of the abdominal and lumbal musculature. The patient could neither sit up nor maintain a sitting position.

Lower extremities: The right leg could not be raised, the left to 30 degrees. Tonus was decreased. Kernig was negative. Deep and superficial sensibility was intact. All the tendon reflexes were absent. There were no signs of involvement of the pyramidal system.

Laboratory Examination:

Blood Picture	July 13	July 15
Neutrophiles	37.5 %	62.5 %
Eosinophiles	0	0
Basophiles	1.5	1.5
Monocytes	0	3
Lymphoid cells (Mononucleosis cells)	60	32
Lymphoblasts	0	1
Plasma cells	1	0
Number of Leukocytes	8 700	12 800

Blood Chemistry: A positive cephalin-cholesterol flocculation test was found.

Spinal fluid: The liquor was clear, colorless. Pandy and Nonne positive. It contained 33 cells (19 polymorph and 14 mononuclear), 63.3 mg % protein, 427 chlorides, and 56 sugar. Pressure was 10 cm.

E. K. G. Evidence of myocardial damage was observed. Sinus rhythm, heart rate 91, P flat and positive in all leads, PQ: 0.14, QRS: 0.06, QT: 0.32. R dominant and isoelectric intermediary stretches in all leads. T I and II flat and positive, T III indiscernable.

Heterophile Agglutination: Negative on July 13.

Clinical Course

July 14: The paralysis became considerably more extensive. Neither the left arm or leg could be lifted. There was difficulty in swallowing and transitory respiratory difficulty developed.

July 15: Swallowing and respiration seemed normal but the paralysis progressed in all the extremities. The pulse was 120, the patient afebrile.

July 16: During the course of the day respiratory difficulty developed. The pulse was 130. In the evening complete respiratory paralysis developed and the patient was placed in an iron lung where satisfactory results were obtained. The general condition of the patient had considerably declined.

July 17: The patient had spent the night in the iron lung satisfactorily. During the course of the morning it was observed that the swallowing reflex was absent. The patient could barely speak. There was a ptosis of the right upper lid and the right pupil was smaller than the left. The general condition of the patient declined rapidly and death ensued despite efforts with the iron lung.

Pathology Report

Macroscopically: There was a hyperplasia of the cervical, submandibular, axillary, inguinal, paratracheal and isolated mesenteric lymph nodes. A subacute splenomegaly was found (220 g.), with increase of the red pulp.

A severe left scoliosis of the thoracic vertebral column, dilation of the right heart with hypertrophy of the right ventricle, red induration of the lungs, chronic stasis in the organs and aspiratory pneumonia were seen.

C.N.S.: The vessels were engorged, the meninges thin, the veins moderately dilated and the impressions somewhat decreased. On the base of the brain the meninges and vessels were fragile.

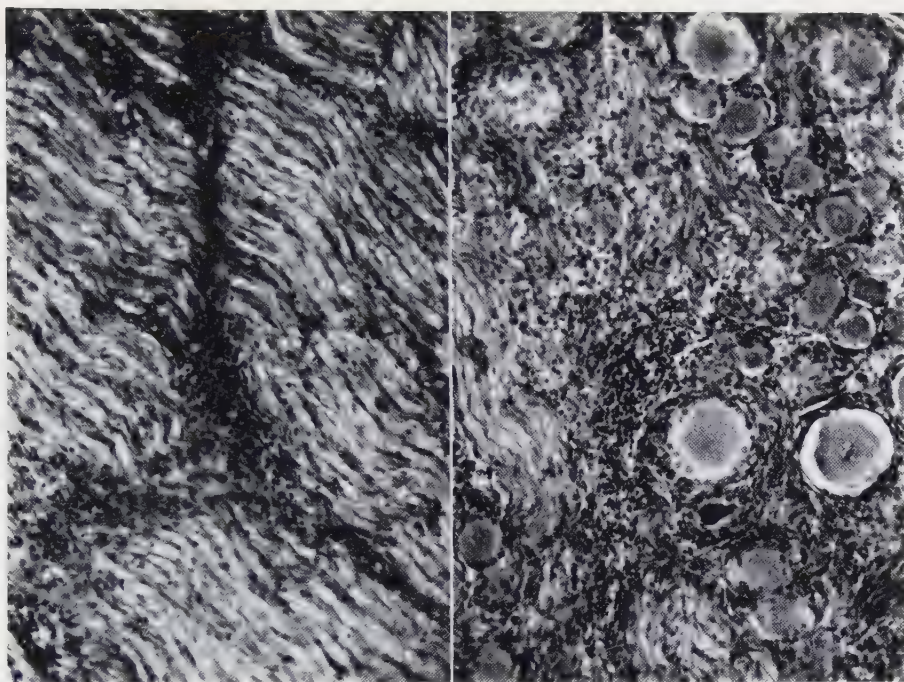
The brain substance was quite moist with moderate engorgement. Cerebellum, pons and medulla oblongata were also hyperemic and moderately edematous.

Microscopic Examination of the Central Nervous System: Cervical spinal cord: Perinuclear clear areas and fixation of the cell membrane of the ganglion cells in the anterior horn were seen. Somewhat lower in the cervical cord a dilation of the central canal, ependyme proliferation and a moderate gliosis was found.

Thoracic cord: The central canal was more strongly dilated.

Lumbal cord: In the nerve roots there are collections of mononuclear cells located primarily perivascularly but also scattered among the nerve fibres. In some areas these cell concentrations are quite massive (Plate 1).

In sections of the spinal ganglion there are also patches of mononuclear infiltra-



I

II

Plate I. Accumulations of mononuclear cells in a nerve root. Mag. 100 $\times$.

Plate II. Mononuclear cell accumulations in a spinal ganglion. Mag. 100 $\times$.

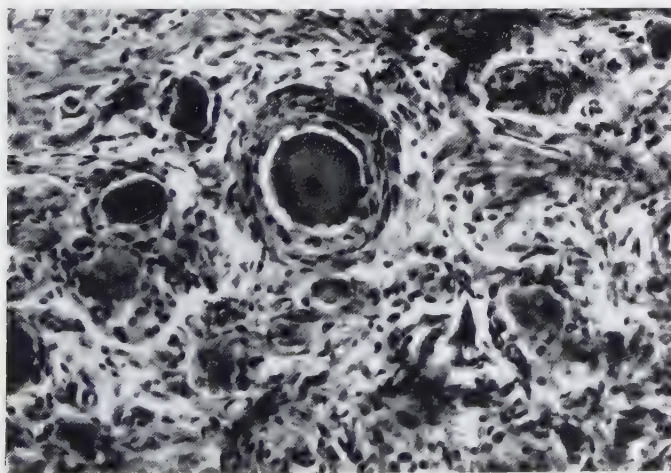


Plate III. Thickening of the ring of capsular cells around the ganglion cells. Mag. 450 $\times$.

tions in which plasma cells are also seen. The capsul cells are occasionally increased and form a thick ring around the ganglion cells (Plates 2 and 3).

In a sudan stained preparation of the roots there are signs of neural sheath degeneration. The Schwann cells clearly contain visible fat substances on both poles of the nuclei. In one area of a hemolan stained preparation large cells with large, somewhat lobated nuclei were seen. A number of smaller cells with pear-shaped to oval nuclei were also seen. These are reactive changes of the Schwann cells.

Microscopic Examination of other Organs: Heart: Cellular infiltrations between the muscle fibres consisting of large round cells with clearly basophilic plasma were seen. These cells resemble those found in the lymph nodes and spleen. There was also a moderate proliferation of the interstitial tissue.

Lungs: The alveoli were of approximately equal size. Most were filled with stab and segmented forms of leukocytes and alveolar wall epithelium. In several areas moderately numerous giant cells with round to elliptical nuclei were found haphazardly scattered. In the immediate area of these cells were found several lymphocytes and plasma cells. The septi were of variable thickness and showed prominent, engorged capillaries, collagenous fibres and infiltration of many mononuclear cells and polymorphonuclear leukocytes. The picture strongly resembles an interstitial pneumonia. The bronchioles had normal mucous membranes but were filled with leukocytes. The lamina propria also showed leukocyte infiltrations.

Liver: The lobular structure was unclear in some areas. There were numerous Glisson sheaths which appear widened by extensive infiltrations of round cells, the nature of which cannot be clearly defined. Some plasma cells were seen. A large number of Kupfer cells were also observed which seemed to be larger than normal. The reticulum between the liver cells was converted to collagenous fibres. Many of the infiltrations appeared very similar to what is seen with lymphatic leukemia of the liver. Where the cellular accumulations are more clearly defined, they can be seen to be basophilic mononuclear cells similar to those found in the lymph nodes.

Kidneys: There were numerous glomeruli with engorged capillaries. Occasionally a hyalinized glomeruli was seen in the area of which lymphocytes were seen. The interstitial tissue was infiltrated with lymphocytes and plasma cells, primarily perivascularly. The vessels themselves showed no pathological changes.

Spleen: Many medium sized and round to elliptical follicles without reaction centers, were seen. The follicle arteries had somewhat thickened walls. The red pulp was abundant and in it were seen many large basophilic, mononuclear cells, similar to those seen in other organs.

The sinus endothelium was prominent. A proliferation of reticulum cells containing a moderate amount of hemosiderin was seen.

Tonsils: There was a strong nodular proliferation of the lymphatic tissue which occasionally showed lighter centers. These centers contained small and large Lymphocytes. Also seen were cells with large, round, somewhat indented, chromatin poor nuclei. There were very few crypts. The epithelium was variably reticulated, somewhat more in the crypts where it was penetrated by lymphocytes and an occasional polymorphonuclear leukocyte.

Axillary lymph nodes: There was a nodular hyperplasia of the lymphatic tissue which occasionally showed lighter centers. The lymph sinuses were clearly defined and contained erythrocytes, lymphocytes and a few polymorphonuclear leukocytes and large cells with large oval nuclei. In some areas the number of plasma cells were

distinctly increased, especially in the immediate area of the marginal sinuses. The smaller sinuses showed many plasma cells and in addition many mononuclear cells with a basophilic plasma. The nodes showed a sinus catarrh with sloughed off sinus endothelium.

Abdominal lymph nodes: A diffuse increase of the lymphatic tissue which showed a nodular structure in the periphery, was seen. The tissue consisted primarily of small lymphocytes among which were found large cells with round chromatin rich nuclei. The lymph sinuses were occasionally clear with a flat endothelium consisting of large round cells with round and elliptical chromatin rich nuclei lying next to the small lymphocytes.

Bone Marrow: A normal leuko- and erythropoiesis was seen. Granulomas as described by *Sundberg* and *Schleicher* were not seen.

Discussion

Although the hospital course was brief, the disease can be considered to have had a course of 18 days. It is interesting to note that on the eleventh day the patient was subjectively free of symptoms, and it was not until the following evening that the neurological symptoms developed and the patient was brought to the hospital. This is similar to the case reported by *Creaturo*, where the neurological symptoms developed on the day of the hospital release. This period of latency between the time of infection and the development of the neurological complications is seen with practically every case reported.

Many authors regard this period, which varies from two to three weeks, as a period of sensitization which forms the basis for the neurological complications. The neuro-allergic explanation of *Pette* and *Barnwarth*, for the Guillain-Barré syndrome has been critically analyzed by *Kazmeier*, who contend that he finds the same symptomatology and histological picture in a pure toxic polyneuritis which he feels is a result of the direct action of the toxin on the tissues with secondary reaction localized in the nerve roots. The latent period of two to three weeks seen following intoxication with triorthocresylphosphate he explains as being the amount of time necessary for the lesions of the myelin sheaths to develop. Whether the postinfectious Guillain-Barré syndrome is also the result of toxic action on the nervous tissues cannot be stated with certainty, and *Kazmeier* concludes by saying there cannot be a single pathogenesis for this syndrome.

The spinal fluid of our patient showed an elevation of protein and cells. In the original description of the syndrome a dissociation be-

tween the protein and cells was described, high protein and no cells. The cases surveyed showed an increase in cells and/or protein. It may be that the dissociation is found in those cases where an allergic mechanism is involved, but where an infection, a toxic effect or intoxication is involved, it does not regularly occur. The cells were only slightly increased as compared to other infectious types of meningitis, for example polio and tuberculosis.

It is further possible that a marked dissociation is only demonstrable in the early stages of the condition.

A demonstration of the heterophile antibodies in the spinal fluid of patients with nervous system involvement has not been noted. However, in a routine check of mononucleosis patients only one of whom showed neurological symptoms clinically, *Silberstein et al.* by means of a modified method were able to show the presence of heterophile antibodies in the spinal fluid of six patients.

Lyons and Harrison examined the spinal fluid of twenty patients with infectious mononucleosis and found abnormal elevations of cells and/or protein with or without neurological symptoms. Although neurological symptoms are by no means obligatory, the neurotropic nature of the infectious agent is conclusively indicated.

The blood picture of our patient was typical. The first smears were obtained on the fourteenth day of illness and it may well be that the blood changes may already have been in regression. The atypical lymphoid or monocytoid cells seen in the peripheral blood bore a striking resemblance to those seen in the lymph nodes and other organs.

The neurological symptoms as observed in the case reported here and those included in the survey show a fairly wide range of variation. Our patient did not show the sensibility disturbances seen in most patients, but involvement of the cranial nerves which is consistently observed, developed shortly before death.

The patient died despite efforts with the iron lung. The two cases reported by *Ricker* likewise died of respiratory failure and as such the entire clinical course of these patients can be classified in the Guillain-Barré Landry group with the least confusion.

The histological studies show the diffuse nature of the disease. The mononucleosis cells occurred extensively, comparable to what has been found by other authors in cases where other organ systems were involved, as well as in those with nervous system involvement. The changes in the lymph nodes correspond closely to those noted by

Downey and Stasney. These investigators removed lymph node material at various stages of the disease and observed the formation of the basophilic cells, reticulum proliferation and in some areas a picture resembling lymphatic leukemia. They found further, many cells which were described as transitional forms of extremely basophilic plasma cells to lymphocytes. In our observations there is also an abundance of atypical cells similar to those seen by *S. Moeschlin* in previous histological examinations of sternal, lymph gland and spleen puncture material from infectious mononucleosis patients where transitional, mature and monocytoid cells were observed. These cells may develop in many organs besides the lymphatic system as in the liver (*van Beeck and Haex, Dolgopol and Husson*) the meninges (*Huber and Gsell*) and in the lungs and kidney (*Ziegler*).

Downey and Stasney are of the opinion that these immature cells are capable of escaping into the peripheral blood. The origin of the collection of these cells peri- and extravascularly is still a matter for conjecture. *Custer and Moeschlin* are of the opinion that they are metaplastically evolved and not infiltrated because of the typical transitional forms and the numerous mitotic figures of these cells observed in situ. Many authors now believe these cells to stem from a generalized reaction of the reticulo-endothelium. Reference to the latter will be made in the discussion of the pathogenesis.

The histological sections of the nerve roots and the spinal ganglia clearly show the collections of atypical basophilic cells, lymphocytes and plasma cells. Such lesions were also found by *Ricker*. The Schwann cell reaction as shown by *Haymaker and Kernohan*, to develop by the thirteenth day, was also observed.

Etiology

The etiology of infectious mononucleosis has long been sought, and today the evidence accumulated indicates fairly conclusively that a virus is involved. In 1926, *Murray, Webb and Swann* found that the bacteria monocytogenes caused a disease with a very pronounced monocytosis in rabbits. *Bland* after producing the disease by transferring blood from a patient to a rabbit, inferred that a toxoplasmosis was involved.

Burnet and Anderson were able to agglutinate erythrocytes sensitized by the virus of Newcastle disease with serum from patients with infectious mononucleosis. The latter evidence gave considerable

substance to the virus theory. Direct demonstration as yet is absent and whether one specific infectious agent is involved is also yet to be shown. If such an infectious agent does exist, pathological research shows an affinity for the reticuloendothelial system. *Schmidheiny* and *Schwarz* speak of a "lymphotropic" agent.

Verlinde, *Sonnville* and *Makstieniks* have further attempted to show the virus etiology by transferring a suspension of lymph node material from an infectious mononucleosis patient to monkeys by means of subcutaneous, intramuscular, intraperitoneal, and intracerebral injections. There followed an increase of heterophile titer, a monocytosis with beginning leukocytosis which was replaced by leukopenia, several fever attacks and in general the picture of an abortive infectious mononucleosis. These authors are certain of the virus etiology and maintain that droplet infection is the means of spread.

The Guillain-Barré syndrome is seen following certain infectious diseases, intoxications, or as a primary disease with no other characteristic prodromal signs. In fatal cases lesions are found, but a specific agent has not yet been found. This is also true where the syndrome occurred in patients with infectious mononucleosis.

In some cases presenting the Guillain-Barré syndrome, *Coxsackie* virus has been isolated, e. g. by *Forrester* and *Tobin* in a case showing the dissociation in the spinal fluid, as well as in a typical case of Guillain-Barré syndrome by *A. J. Rhodes* and in other cases by *Bernkopf*.

The question, posed by *Epstein* and *Dameshek* in 1931, of which is primary, the nervous system involvement or the involvement of the lymphatic system, still commands attention. The reticuloendothelial reaction is not a specific reaction, occurring in other diseases, so that it can be hypothesized that an infectious agent capable of producing such a reaction and having neurotropic character could be responsible for the neurological complications. The infectious agent causing the clinical picture of infectious mononucleosis could also well be a widespread neurotropic virus causing neurological symptoms occasionally, when as yet unknown conditions exist; for example, as is believed to be the case with poliomyelitis virus and coxsackie virus. These conditions could be created by the presence of other infectious agents which act as a pacemaker for a neurotropic virus, in a sense opening the portals to the nervous systems for the virus, which may be present in apparently normal individuals; or certain physical fac-

tors such as excessive exposure to the sun, cold trauma and exhaustion may provide the conditions necessary as is known to occur with the herpes virus.

Pathogenesis

The most recent studies show that a generalized reaction of the reticulo-endothelial system is involved in all cases of infectious mononucleosis. *Moeschlin* by means of lymph gland and spleen puncture analysis indicated that the essential feature of the reticulo-endothelium reaction was the large lymphatic reticulum cells developing into the lymphoid monoblasts. In the spleen the cells develop from the reticulo-endothelium of the follicles. The occurrence of extensive accumulations of reticulo-endothelial elements in other organs has already been mentioned. This evidence has led some authors to speak of a "secondary reactive reticulosis". This reaction however, is not specific as reported by *Gardner* and *Paul*. The reticulo-endothelial reaction is observed with such diseases as grippe, pappataci fever, dengue fever and especially hepatitis epidemica. With infectious mononucleosis the reaction is more exaggerated however. The question of how the local organ lesions develop still remains open, but it seems probable the some viruses with a special tropism toward the reticulo-endothelial system are able to produce these reactions.

Acknowledgements

I wish to express my gratitude to Dr. S. *Moeschlin* for suggesting the theme and his considerate guidance. Further I wish to thank the Zürich University Medical Clinic (Director Prof. Dr. W. *Löffler*) for permitting the use of the case history; Prof. *Zollinger* of the Pathology Institute of the Zürich Cantonal Hospital for the use of their pathology reports, histological sections and micro-photographs; and Prof. F. *Lüthy* and P.-D. Dr. S. *Moeschlin* for their histological studies.

Summary

Clinical and pathological observations have shown infectious mononucleosis to be a generalized disease in which any organ can be involved. The association of the Guillain-Barré syndrome with infectious mononucleosis presents one of the possible neurological complications. A survey of cases and the study of a fatal case showing cellular infiltration in the spinal ganglia and dorsal and ventral nerve roots has been presented. This, as well as the other neurological complications of infectious mononucleosis, may be the result of a specific virus either the same one that causes the clinical picture of infectious mono-

nucleosis or one capable of producing the same reticulo-endothelial reaction. The same underlying cause for all the neurological complications must exist, the localisation determining the symptomatology.

Zusammenfassung

Klinische und pathologische Beobachtungen haben ergeben, daß es sich bei der Mononucleosis infectiosa um eine allgemeine Erkrankung handelt, bei welcher jedes Organ betroffen sein kann. Das Zusammenreffen von Guillain-Barré-Syndrom mit Mononucleosis infectiosa stellt eine der möglichen neurologischen Komplikationen dieser Krankheit dar. Es wurde eine Übersicht über die Fälle erteilt und ein letaler Fall besonders behandelt, der zelluläre Infiltrationen in den Spinalganglien, den vorderen und den hinteren Wurzeln zeigte. Letztere sowie die anderen neurologischen Komplikationen der Mononucleosis infectiosa dürften das Resultat eines spezifischen Virus sein, entweder desselben, welches das klinische Bild der Mononucleosis infectiosa verursacht, oder eines, welches die gleiche reticulo-endotheliale Reaktion hervorzurufen vermag. Für jedes Betroffene des Nervensystems muß dieselbe Grundursache angenommen werden, wobei die Symptomatologie durch die Lokalisation bestimmt wird.

Résumé

Les observations cliniques et anatomo-pathologiques ont montré que la mononucléose infectieuse est une maladie générale et peut atteindre tous les organes. L'association du syndrome du Guillain-Barré avec la mononucléose infectieuse est une des complications neurologiques possible. Révision des cas et l'étude d'un cas mortel montrent une infiltration cellulaire du ganglion et des racines nerveuses antérieures et postérieures. Cette et autres complications neurologiques de la mononucléose infectieuse sont peut-être dues à un virus spécifique, le même qui produit le tableau clinique de la mononucléose infectieuse d'un autre capable de produire la même réaction réticulo-endothéliale. Il doit exister une même cause pour tous ces manifestations neurologiques, la localisation déterminant la symptomatologie.

Bibliography

- Beek van, C. A., and A. J. Haex: Ned. Tijdschr. Geneesk. 87, No. 30/31, 1943. — Bernkopf, H.: J. Amer. med. Ass. 145, 1215, 1951. — Bernstein, T. C., and H. G.

- Wolf: 33, 1120, 1950. — Bland, J. O. W.: Lancet 2, 521, 1930. — Bradshaw, R. W.: Ohio St. Med. J. 27, 717, 1931. — Burnet, F. M., and S. G. Anderson: Brit. J. exp. Path. 27, 236, 1946. — Burns, J. E.: Arch. intern. Med. 4, 118, 1909. — Contratto, A. W.: Arch. intern. Med. 73, 449, 1944. — Coogan, T. S., D. L. Martinson and W. H. Mathew: Ill. med. J. 87, 296, 1945. — Creaturo, N. E.: J. Amer. Med. Assoc. 143, 234, 1950. — Custer, R. P., and E. B. Smith: Blood 3, 830, 1948. — Dolgopol, V. B., and G. S. Husson: Arch. Int. Med. 83, 179, 1949. — Downey, H., and J. Stasney: Folia Haematol. 54, 417, 1936. — Epstein, S. H., and W. Dameshek: New Engl. J. Med. 205, 1238, 1931. — Fiese, M. J., S. Cheu and J. Radding: Arch. Int. Med. 92, 438, 1953. — Filatow: Infektiöse Krankheiten des Kindesalters. Moskau 1885. — Forrester, K. M., and J. O'H. Tobin: Lancet 1951, II, 663. — Gall, E. A.: and H. A. Stout: Amer. J. Path. 16, 433, 1940. — Gardner, H. T., J. R. Paul: Yale J. Biol. Med. 19, 839, 1947. — Garvin, J. S.: J. Amer. Med. Ass. 1953, 24. — Geliebter, S.: Lancet 160, 753, 1946. — Glanzmann, E.: Das Lymph Amoide Drüsen Fieber, Berlin 1930. — Graham, S. D., W. H. Schwartz and W. L. Chapman: U.S. Naval Med. Bull. 49, 914, 1949. — Gsell, O.: Dtsch. med. Wschr. 1937, 1759, 2. — Guillain, G., J. A. Barré and A. Strohl: Bull. Soc. méd. Hôp. Paris 40, 1462, 1916. — Haymaker, W., and J. W. Kernohan: Medicine 28, 59, 1949. — Hiller, R. I., and M. S. Fox: Marquette med. Rev. 7, 152, 1943. — Huber, W.: Schweiz. med. Wschr. 1938, 892. — Johansen Hecht, A.: Acta med. scand. 76, 269, 1931. — Kazmeier, F.: Dtsch. Z. Nervenheilk. 160, 10, 1949. — Klovstad, O.: Acta med. scand. 138, 60, 1950. — Landry, O.: Gaz. hebdom. Méd. 6, 472, 1895. — Lehdorff und Schwarz: Das Drüsen-Fieber. Ergebn. Inn. Med. 42, 775, 1932. — Longcope, W. T.: Am. J. med. Sci. 164, 781, 1922. — Lyons, H. A., and J. G. Harrison: Blood 4, 734, 1949. — Moeschlin, S.: "Spleen Puncture", Grune & Stratton, New York, P. 87, 1951. — Moeschlin, S.: Dtsch. Arch. klin. Med. 187, 249, 1941. — Murray, Webb and Swann: J. Path. Bact. 29, 407, 1926. — Nixon, Jr., K. Robert: Ill. med. J. 102, 316, 1952. — Nyfeldt, A.: C. R. Soc. Biol. Paris 33, 218, 1935. — Owen, Jr., F. William: An. West. Med. and Surg. 6, 156, 1952. — Paul and Bunnel: Amer. J. med. Sci. 183, 90, 1932. — Pette, H.: Ges. inn. Med. 55, 92, 1949. — Pfeiffer, E.: Jb. Kinderhk. 29, 257, 1889. — Rhodes, A. J., E. M. Clark, D. S. Knowles, E. S. Shimada, R. G. Ritchie and W. L. Donohue: Canad. J. Pub. Health. 41, 183, 1950. — Ricker, W., A. Blumberg, C. H. Peters and A. Widerman: Blood 2, 217, 1947. — Sabin, A. B., and C. D. Aring: Amer. J. Path. 17, 469, 1941. — Schmidheiny: Schweiz. med. Wschr. 1927, 241. — Silberstein, J. K., T. C. Bernstein and T. Stern: J. Lab. clin. Med. 33, 1204, 1948. — Silversides, J. L., and J. C. Richardson: Canad. med. Ass. J. 63, 138, 1950. — Slade, J.: Involvement of the Central Nervous System in Infectious Mononucleosis, New Engl. J. Med. 234, 753, 1946. — Sprunt and Evans: Bull. Johns Hopk. Hosp., 31, 410, 1920. — Schleicher, E. M.: Acta haemat. 2, 242, 1949. — Schmidt, V., and T. A. Nyfeldt: Acta oto-laryng. 26, 680, 1938. — Tidy, H. L.: Lancet 1934, 180. — Tidy: J. Hem. III, 823, 1948. — Türck: Wien. klin. Wschr. 1907, 151. — Verlinde, J. D., L. M. de Sonnaville and Makstenieks: Leeuwenhoek 16, 21, 1950. — Ziegler, E.: Arch. Pathology 37, 196, 1944. — Zohman, B. L., and E. G. Silverman: Ann. intern. Med. 16, 1233, 1942.

Autobiography

I was born in Brooklyn, New York, U.S.A. on August 4, 1925. My education was pursued in the public school system of that city. During the war I served as a surgical technician in an army hospital from 1944 to 1946. Resuming my premedical studies I obtained a Bachelor of Arts Degree from Brooklyn College in 1948. After working in food analysis laboratory for one year I entered Zurich University Medical School in 1949 where I obtained my degree in 1954.